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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/804,457	03/12/2001	Michael P. Maher	AUROBIO.026A	8759

20995 7590 10/21/2002

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
MURPHY, JOSEPH F	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 10/21/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)	
09/804,457	MAHER ET AL.	
Examiner	**Art Unit**	
Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4, 5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-29 in Paper No. 7, 7/30/2002 is acknowledged. Claims 30-48 were cancelled in Paper No. 7, 7/30/2002. Claims 1-29 are pending and under consideration.

Specification

The disclosure is objected to because of the following informalities: The U.S. patent applications which are to be incorporated by reference are not listed on page 1, lines 10-21.

Appropriate correction is required.

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "insignificant" in claim 24 is a relative term which renders the claim indefinite. The term "insignificant" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably

apprised of the metes and bounds of the invention. Claim 25 is rejected insofar as they depend on the recitation of the term "insignificant".

Claim 1 is vague and indefinite in the recitation of the term "biological activity". The term "biological activity" is not defined by the claim, but give no definition of what this activity is. Various biological activities can be attributed to a compound. For example, "activity" could constitute transportation throughout a cell, effects on osmotic pressure, or non-specific binding.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzalez et al. (1995) in view of Reiner et al. (1995).

Gonzalez et al. teaches a method for achieving fast ratiometric voltage-sensitive fluorescence changes in single cells using fluorescence resonance energy transfer. The mechanism is based on hydrophobic fluorescent anions that rapidly redistribute from one face of the plasma membrane to the other according to the Nernst equation (Gonzalez at 1272). In this method L-M(TK-) fibroblasts were loaded with DISBAC(3), a fluorescent dye to monitor membrane potential transients, and coated with fluorescein-labeled wheat germ agglutinin (Ibid. at 1273), this pair serves as the donor-acceptor pair for the energy transfer. The L-M(TK-) cells have low background currents (Ibid. at 1275). The method teaches the measurement of fluorescent changes of the DISBAC(3) in response to voltage changes (Ibid at 1276, Figure 4). The change in the transmembrane potential is measured without the use of the patch clamp technique. In this Figure, the voltage steps are applied with the patch clamp technique, while the output is measured by monitoring the fluorescence. The electric field would not vary over the area of observation, which in this case is a single cell. Gonzalez further teaches monitoring the fluorescence intensity changes, indicative of membrane potential, in response to square wave step depolarizations from the -70 mV holding potential to 40, 80, 120 and 160 mV (Ibid at 1277, Figure 6). Again, the voltage steps are applied with the patch clamp technique, while the indicia of membrane potential is the fluorescence intensity. The step potentials are applied for 500 milliseconds. Gonzalez et al. further teaches the practice of this method in neonatal cardiac myocytes, which comprise voltage gated ion channels, which are activated upon depolarization (Ibid. at 1278, Figure 8).

Gonzalez does not teach characterizing the effect of a compound on ion channel activity of a compound with this method. Renier et al. teaches a method to evaluate expression of functional CFTR. The technique uses the potential-sensitive probe DISBAC2(3), by single-cell fluorescence imaging. The DISBAC(3) method was first validated on the mouse mammary tumor cell line C127, stably expressing wild-type CFTR (Renier at 1278, Figure 1). Activation of protein kinase A by the cAMP-permeable analogue 8-Br-cAMP induced cell membrane depolarization consistent with expression of wild-type CFTR. The effect of 8-Br-cAMP on A549 cells transfected with adenovirus encoding CFTR was then measured (Ibid. at 1279, Figure 2). Therefore, it would have been obvious to one of skill in the art at the time the invention was made to practice a method of characterizing the effect of a compound on ion channel function by exposing a cell expressing the ion channel to alterations in the electric field and measuring the effect on the membrane potential with fluorescent dyes. The motivation is provided in the Renier reference which teaches that the DISBAC(3) method is quick, simple, and reproducible, and does not require invasive cell loading procedures (Ibid. at 1275). The expectation of success is provided in the Gonzalez reference which teaches that voltage indicators based on FRET may already be practically useful and that modest, rationally attainable improvements in sensitivity and speed could make them superior for many biological applications.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph F. Murphy whose telephone number is 703-305-7245. The examiner can normally be reached on M-F 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
October 8, 2002

Notice of References Cited	Application/Control No. 09/804,457	Applicant(s)/Patent Under Reexamination MAHER ET AL.	
	Examiner Joseph F Murphy	Art Unit 1646	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
*	U	Gonzalez JE, Tsien RY.Voltage sensing by fluorescence resonance energy transfer in single cells.Biophys J. 1995 Oct;69(4):1272-80.
√	V	Renier M, et al. Use of a membrane potential-sensitive probe to assess biological expression of the cystic fibrosis transmembrane conductance regulator. Hum Gene Ther. 1995 Oct;6(10):1275-83. √
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

FORM PTO-1449

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(USE SEVERAL SHEETS IF NECESSARY)

ATTY. DOCKET NO. AUROBIO.026A	APPLICATION NO. 09/804,457
APPLICANT Maher, et al.	
FILING DATE March 21, 2001	GROUP 1645

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE (IF APPROPRIATE)
	1	4,072,578	2/7/78	Cady, et al.			
	2	4,514,500	4/30/85	Giaever, et al.			
	3	4,461,304	7/24/84	Kuperstein			
	4	4,628,933	12/16/86	Michelson			
	5	4,677,989	7/7/87	Robblee			
	6	4,969,468	11/13/90	Byers, et al.			
	7	5,024,233	6/18/91	Chow			
	8	5,178,161	1/12/93	Kovacs			
	9	5,187,096	2/16/93	Giaever, et al.			
	10	5,405,367	4/11/95	Schulman, et al.			
	11	5,432,086	7/11/95	Fränzl, et al.			
	12	5,439,440	8/8/95	Hofmann			
	13	5,545,130	8/13/96	Hofmann, et al.			
	14	5,563,067	10/8/96	Sugihara, et al.			
	15	5,571,158	11/5/96	Bolz, et al.			
	16	5,810,725	9/22/98	Sugihara, et al.			
	17	5,855,801	1/5/99	Lin, et al.			
	18	5,935,155	8/10/99	Humayun, et al.			
	19	5,957,958	9/28/99	Schulman, et al.			
	20	5,965,452	10/12/99	Kovacs			
	21	5,981,268	11/9/99	Kovacs, et al.			
	22	6,008,038	12/28/99	Kröger, et al.			
	23	6,009,347	12/28/99	Hofmann			
	24	6,024,702	2/15/00	Iversen			
	25	6,031,711	2/29/00	Tennent, et al.			
	26	6,038,478	3/14/00	Yuen, et al.			
	27	6,046,002	4/4/00	Davis,et al.			

EXAMINER	DATE CONSIDERED 10/30/02

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PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(USE SEVERAL SHEETS IF NECESSARY)

ATTY. DOCKET NO.	APPLICATION NO.
AUROBIO.026A	09/804,457
APPLICANT: Maher, et al.	
FILING DATE: March 21, 2001	GROUP: 1645

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE (IF APPROPRIATE)
	28	6,051,422	4/18/00	Kovacs, et al.			
	29	6,063,260	5/16/00	Olesen, et al.			
	30	6,099,960	8/8/00	Tennent, et al.			
	31	6,205,016	3/20/01	Niu			

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EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	32	WO97/05922	2/20/97	PCT				
	33	WO00/25121	5/4/00	PCT				
	34	WO00/68686	11/16/00	PCT				
	35	1 067 378 A1	1/10/01	EPO				

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	36	Arndts, Oral Presentation Abstract, Second International Cell Analysis Products Users Meeting in Hilton Head Island, South Carolina, USA (June 3-5, 1998).
	37	Barr and Plonsey, Biophys. J. 61, 1164-1175 (1992).
	38	Barr and Plonsey, IEEE 42, 1185-11911 (1995).
	39	Cartee and Plonsey, Med & Biol. Eng. & Comp. 30 389-398 (1992).
	40	Cartee and Plonsey, IEEE 39, 76-85 (1992).
	41	Eppich et al., Nature Biotech. 18, 882-887 (2000).
	42	Greenberg, et al. IEEE 46, 505-514 (1999).
	43	Gross, et al. Biophys. J. 50, 339-348 (1986).
	44	Jentsch and Günther, BioEssays 19, 117-126 (1997).
	45	Klee and Plonsey, Biophys. J. 12 1661-1675 (1972).
	46	Klee and Plonsey, IEEE 23, 347-354 (1976).
	47	Mitchell et al., J. Biomed. Eng. 14, 52-56 (1992).
	48	Plonsey, Med & Biol. Eng. & Comput. 19 311-315 (1981).
	49	Plonsey, Med. & Biol. Eng. & Comput. 33 337-340 (1995).

EXAMINER	DATE CONSIDERED 10-1-02

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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ATTY. DOCKET NO.	APPLICATION NO.
AUROBIO.026A	09/804,457
APPLICANT	
Maher, et al.	
FILING DATE	**GROUP**
March 21, 2001	1645

EXAMINER INITIAL		OTHER DOCUMENTS (INCLUDING AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.)
	50	Plonsey and Barr, IEEE 42 329-336 (1995).
	51	Plonsey and Barr, IEEE 9/10 130-137 (1998.)
	52	Rattay, Neuroscience 89 335-346 (1999).
	53	Roth, Critical Reviews in Biomed. Eng. 22 263-305 (1994).
	54	Rowell, Biophotonics Int. 12 25-26 (2000).
	55	Schmidt et al., Proc. Natl. Acad. Sci. USA 94 8948-8953 (1997).
	56	Stone et al., J. Cardiovascular Electrophysiology 10 92-107 (1999).
	57	Svirskis et al., American Phys. Soc. 0022-3077 579-586 (1997).
	58	Tung and Borderies, Biophys. J. 63 371-386 (1992).
	59	Tung et al., Circulation Research 69 722-730 (1991).
	60	Zhou, et al., Circulation Research 83 1003-1014 (1998).

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EXAMINER	DATE CONSIDERED 10-2-02

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FORM PTO-1449 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO. AUROBIO.026A	APPLICATION NO. 09/804,457
SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT BY APPLICANT (USE SEVERAL SHEETS IF NECESSARY)	APPLICANT Maher, et al.	
	FILING DATE March 12, 2001	GROUP 1645

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE (IF APPROPRIATE)

FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	1.	96/41166	12/19/96	PCT				

EXAMINER INITIAL		OTHER DOCUMENTS (INCLUDING AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.)
	2.	González, J.E., et al., "Cell-based assays and instrumentation for screening ion-channel targets", Drug Discover Today, Vol. 4, No. 9, pp. 431-439, (September 1999).
	3.	González, J.E., et al., "Voltage sensing by fluorescence resonance energy transfer in single cells", Biophysical Journal, Vol. 69, No. 4, pp. 1272-1280, (October 1995).
	4.	Giuliano, K.A., et al., "Fluorescent-protein biosensors: new tools for drug discovery", Trends In Biotechnology", Vol. 16, No. 3, pp. 135-140, (March 1998).

EXAMINER	DATE CONSIDERED 10-3-02

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